REMARKS

I. Telephonic Examiner's Interview

Applicants thank Examiner Wang and Examiner Saoud for the courtesies extended in the telephonic interview held on August 13, 2008 with Applicants' attorneys. The 103 rejection was the sole issue. The first point that was addressed was that neither Studer nor Lee teaches sequential exposure of cells to the growth factors as recited in claims 1 and 13. Examiner Wang stated that the end result was the same and that, therefore, the method was obvious. Applicants' attorneys pointed out to Examiner Wang that the claim was not directed to the end result, but was directed to a method. Applicants' attorneys inquired why, just because the end result is the same, a different method would be obvious. The Applicants' attorneys' position was that the mere fact that the end result is the same is not legally sufficient to render a different method of achieving the same result obvious. Examiner Saoud indicated that they would reconsider this after receiving a response.

Next, Applicants' attorneys pointed out that the references do not teach co-culturing with astrocytes, either. They pointed out that the methods disclosed in the cited references do not result in cells per step (c) that are then exposed to astrocytes. With the referenced methods, the cells that are exposed to the growth factors differentiate into astrocytes. They are not co-cultured with astrocytes. In the claimed methods, after the cells are exposed to the factors they are then co-cultured with astrocytes. Therefore, with the claimed method the astrocytes are not derived from the cells that were exposed to the factors, but are independently administered to the cells that were first exposed to the factors.

Examiner Wang then stated that the rejection is not one of anticipation, but one of obviousness. Applicants' attorneys, therefore, asked the Examiner the following question. Given a procedure where cells become astrocytes, what would have made it obvious to expose those cells to astrocytes? Examiner Saoud said they would reconsider the matter.

II. Status of the Claims

Claims 1-11 and 13 are currently pending. Claims 2, 3, 7 and 8 have been amended. The term "MAPC" has been explicitly recited to avoid any potential for indefiniteness of an acronym. No new matter is added with these amendments.

III. Sequence Rules

On page 2 of the Office Action, The Examiner is requiring sequence identification for the amino acids and nucleic acids presented in Figure 4 and Table 1 of the specification, a substitute computer readable form (CRF) copy, and a hard copy of a Sequence Listing, and a Sequence Amendment entering the paper copy of the Sequence Listing.

Table 1 and Figure 4 have been amended to include sequence identifiers. Applicants also submit concurrently herewith a substitute computer readable form (CRF) copy and a hard copy of a Sequence Listing, and a Sequence Amendment entering the paper copy of the Sequence Listing.

IV. Information Disclosure Statement (IDS)

On page 4 of the office Action, the Examiner is requiring an IDS. Applicants will submit an IDS forthwith.

V. Specification

On page 5 of the Office Action, the Examiner is requiring that all use of trademarks in the specification be capitalized and accompanied by generic terminology. The specification has been amended to conform with this requirement.

VI. The Rejections

A. Rejection Under 35 U.S.C. § 112, Second Paragraph

On page 5 of the Office Action, claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because the claim contains the trademark/trade name N2 supplement®.

Claim 3 has been amended to delete the trademark symbol, and thus this rejection is obviated.

B. Rejection Under 35 U.S.C. § 103(a)

On page 6 of the Office Action, claims 1-7, 9, 11 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over WO02/086073 (Studer et al.; hereinafter "Studer") in view of US 2003/0211605 (Lee et al; hereinafter "Lee").

The Examiner asserts, in pertinent part, that Studer teaches a method of inducing stem cells to differentiate in the presence of basic fibroblast growth factor (bFGF), fibroblast growth factor 8 (FGF8), Sonic Hedgehog (SHH), brain-derived neurotropic factor (BDNF) and co-culturing the cells with astrocytes. The Examiner also asserts that Studer teaches expanding embryonic stem (ES) cells in a medium comprised of bFGF, FGF8, SHH, and BDNF. Finally, the Examiner asserts that Studer teaches differentiating cultured ES cells into neurons and astrocytes, "which meets the limitation of 'comprising co-culture astrocytes.'"

With regard to Lee, the Examiner asserts, in pertinent part, that Lee teaches inducing stem cells to differentiate into neuronal cells by culturing ES cells in the presence of bFGF, FGF8, SHH and co-culturing the cells with astrocytes. The Examiner also asserts that Lee teaches expanding ES cells in a medium comprised of bFGF, FGF8 and SHH. Finally, the Examiner asserts that Lee teaches differentiating cultured ES cells into neurons using the same medium as used for expanding the cells, plus ascorbic acid and 3% astrocytes.

Applicants respectfully traverse this rejection for several reasons, discussed below.

1. 35 U.S.C. § 103(a)

To establish a *prima facie* case of obviousness, three standards must be met. First, there must be motivation for one of ordinary skill in the art to modify the reference or to combine reference teachings. Motivation can come from the references themselves and also from the general knowledge in the art. In addition, there must be a reasonable expectation of success. MPEP 2143. Moreover, the combination of references must result in the claimed invention. In the present case, motivation to combine is lacking. And, even if there were motivation to combine, the combination would not result in the claimed invention.

2. The Claimed Invention

The claimed methods of the invention for inducing differentiation of stem cells into neuronal cells require the sequential steps of culturing stem cells with neurotrophic factors, in which the sequential steps are the following: (1) culturing stem cells with bFGF; (2) then culturing the cells produced in the previous step with FGF8 and SHH; (3) then culturing the cells produced in the previous step with BDNF; and (4) finally co-culturing the cells produced in the previous step with astrocytes.

3. Discussion of Studer

Studer teaches, in pertinent part, a five-step method of culturing embryonic stem (ES) cells, in which step four includes placing embryoid bodies in medium supplemented with bFGF, SHH and FGF8 at the same time. In addition, Studer teaches that BDNF can be added either in step four or five. Studer also teaches culturing ES cells to generate astrocytes.

Nowhere does Studer teach or suggest a method for sequentially culturing stem cells first with bFGF; then with FGF8 and SHH; then with BDNF; and finally co-culturing the cells produced from sequential

exposure to those factors with astrocytes, as required by claims 1 and 13. Indeed, Studer provides no motivation to a skilled artisan to modify its teaching to sequentially culture stem cells with the above-described neurotrophic factors of the claimed invention.

In fact, Studer actually teaches away from the claimed invention by stating "to obtain efficient dopaminergic differentiation, the following growth factors are required during stage IV: sonic hedgehog... and FGF8..." (page 25, lines 6-9 of paragraph 76) (emphasis added). Hence, the teaching by Studer of culturing ES cells in media supplemented with SHH, FGF8, bFGF in one step (step four) would not motivate one skilled in the art to modify this teaching to culture stem cells sequentially, as required by claims 1 and 13. In addition, Studer teaches that BDNF can be added either in step four with bFGF, SHH and FGF8, or in step five. Nowhere does Studer teach or suggest the step of culturing stem cells solely in the presence of BDNF, as required by claims 1 and 13.

For the above reasons alone, Studer would not suggest the claimed invention.

But there is another independent reason why Studer would not suggest the claimed invention. The reason is that Studer in no way suggests co-culturing the cells that are produced in the Studer method *with* astrocytes. The Studer cells *become* astrocytes. They are not co-cultured with astrocytes.

The Examiner is also respectfully referred to the discussion in Section I above where Applicants' attorneys discussed these points with the Examiner and her supervisor.

4. Discussion of Lee

Lee does not teach or suggest the methods of the claimed invention in which neurotrophic factors are used in sequential steps to differentiate stem cells into neuronal cells, as described above and as required by claims 1 and 13. Thus, Lee does not compensate for the deficiencies of Studer.

Lee teaches, in pertinent part, a five step method of generating neurons from ES cells in which step four includes expanding CNS precursor cells in a medium that can include bFGF, SHH or FGF8. Lee also discloses optionally including BDNF in step four with bFGF, SHH or FGF8. Finally, Lee discloses using astrocytes in a *neuronal* cell culture which includes about 50% to 85% neurons and about 1% to 3% astrocytes.

Nowhere does Lee teach or suggest sequentially culturing stem cells first with bFGF; then with FGF8 and SHH; then with BDNF; and finally co-culturing the resulting cells with astrocytes, as required by claims 1 and 13. In addition, Lee does not teach or suggest the step of culturing cells solely with BDNF.

Finally, Lee is silent with respect to co-culturing cells with astrocytes to cause differentiation. Rather, Lee merely discloses using astrocytes in a *neuronal* cell culture that includes about 50% to 85% neurons and about 1% to 3% astrocytes.

The Examiner is also respectfully referred to the discussion in Section I above where Applicants' attorneys discussed these points with the Examiner and her supervisor.

Accordingly, neither Studer nor Lee teaches or suggests the claimed sequential method. Therefore, even if there were motivation to combine Studer with Lee, the claimed invention would not be the result because the combination of Studer and Lee would not produce a *sequential* method of inducing differentiation of stem cells into neuronal cells. Nor would the combination produce a method in which the cells that are exposed to the factors are then co-cultured *with* astrocytes.

In summary, neither Studer nor Lee would have motivated the person of ordinary skill in the art to modify the methods that they reported (i.e., to expose the cells to the factors sequentially) because the method was adequate as it was. Nor would the combination produce a method in which the cells that are exposed to the factors are then co-cultured with astrocytes. Thus, Studer or Lee or a combination of Studer and Lee would not produce the method of claims 1 and 13.

In view of these points, Applicants submit that at least two of the requirements for supporting a *prima facie* case of obviousness have NOT been met. Based on the foregoing, Applicants respectfully request withdrawal of this rejection.

Claims 2-11 depend directly from claim 1, and thus they too are deemed neither to be taught nor suggested by Studer in view of Lee.

C. Rejection Under 35 U.S.C. § 103(a) of Claims 1-11 and 13

On page 10 of the Office Action, claims 1-11 and 13 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Studer in view of Lee as applied to claims 1-7, 9, 11 and 13 discussed above, and further in view of Song et al. (Methods in Mol. Biol., 2002, 198:79-88; hereinafter "Song").

The Examiner acknowledges that Studer and Lee do not teach multipotent adult progenitor cells and bone marrow cells, as required by claims 7-10, but asserts, in pertinent part, that Song teaches culturing and differentiating bone marrow cells and that bone marrow cells are mesenchymal stem cells or bone marrow stromal cells, which meet the limitations of multipotent adult progenitor cells and bone marrow, as recited in claims 7-10.

Applicants respectfully traverse this rejection.

1. Discussion of Song

Rebuttal of the rejection of claims 1-7, 9, 11 and 13 has been made hereinabove in detail. The disclosure of Song, as implicitly acknowledged by the Examiner, does not cure the deficiencies of Studer and Lee to teach or suggest the claimed invention with respect to claims 1-6, 9, 11 and 13. With regard to claims 7-10, these claims depend directly from claim 1. Thus, because it is submitted that neither Studer nor Lee, either alone or in combination, teaches or even suggests the method recited in claim 1, claims 7-10 also are deemed neither to be taught nor suggested by Studer in view of Lee and further in view of Song. Applicants respectfully request withdrawal of this rejection.

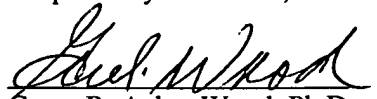
VII. Summary and Conclusions

A person of ordinary skill in the art would not be motivated to modify the teachings of Studer, Lee and Song, or to combine the teachings of Studer, Lee and Song, to come up with the claimed invention because Studer, Lee or Song do not teach or even suggest, alone or combined, sequentially culturing stem cells in which the stem cells are (1) first cultured with bFGF; (2) then cultured with FGF8 and SHH; (3) then cultured with BDNF; and (4) finally co-cultured with astrocytes, as required by claims 1 and 13.

In view of Applicants' amendments and remarks, Applicants believe that the pending claims are in condition for allowance. Early notification to that effect is respectfully requested.

Applicants believe that the fee for a two-month extension of time is due with this filing. Such fee is being simultaneously paid via electronic funds transfer with this submission. The Commissioner is hereby authorized to charge any additional fees required or to credit any overpayment to Deposit Account 20-0809. Applicants hereby authorize the Commissioner under 37 C.F.F. § 1.136(a)(3) to treat any paper that is filed in this application which requires an extension of time as incorporating a request for such an extension.

Respectfully submitted,



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